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Enantioselective Copper-Catalyzed Reductive Coupling of Alkenylazaarenes with Ketones

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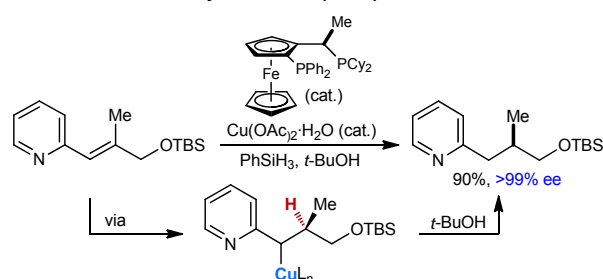
ABSTRACT: Catalytic enantioselective methods for the preparation of chiral azaarene-containing compounds are of high value. By combining the utility of copper hydride catalysis with the ability of C=N-containing azaarenes to activate adjacent alkenes toward nucleophilic additions, the enantioselective reductive coupling of alkenylazaarenes with ketones has been developed. The process is tolerant of a wide variety of azaarenes and ketones, and provides aromatic heterocycles bearing tertiary-alcohol-containing sidechains with high levels of diastereo- and enantioselection.

The development of new catalytic reactions for the functionalization of aromatic heterocycles and their derivatives continues to be a valuable endeavor due to the importance of these structures in natural products, pharmaceuticals, agrochemicals, and other molecules of interest. In this regard, recent efforts from our laboratory have targeted the development of processes that exploit the ability of a suitably positioned C=N moiety within azaarenes to activate adjacent alkenes toward catalytic enantioselective nucleophilic additions.^{1,2,3} The first of these reports described copper-catalyzed reductions⁴ of β,β -disubstituted 2-alkenylazaarenes, which result in alkylazaarenes with a new stereogenic center at the β -carbon (representative example in Figure 1A).¹ Since these reactions likely proceed via the intermediacy of organocopper species that undergo protonation with *t*-BuOH, we questioned whether these intermediates could be trapped in situ with an alternative electrophile such as a ketone (Figure 1B). Such a reductive coupling process would be synthetically more valuable, delivering more complex tertiary-alcohol-containing products with stereochemistry at both α - and β -carbons.

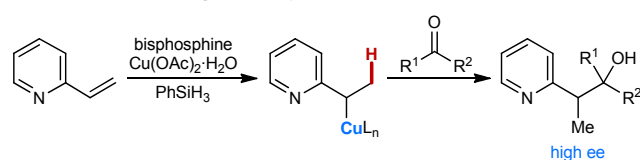
Although the proposed process is related to copper-catalyzed reductive aldol reactions described previously,^{5,6,7,8,9} to our knowledge there are no reports of alkenylazaarenes being employed as substrates in these reactions. To date, the only report of catalytic reductive coupling reactions of alkenylazaarenes is that from the Krische group, who described racemic rhodium-catalyzed hydrogenative coupling of vinylazines with *N*-sulfonylaldimines (Figure 1C).¹⁰ The realization of *enantioselective* variants of this and related processes would therefore be of obvious value. Herein, we report highly enantioselective copper-catalyzed reductive coupling reactions of alkenylazaarenes with ketones.

This study began with examination of the enantioselective reductive coupling of 2-vinylquinoline (**1a**) with acetophenone (1.1 equiv) using PhSiH₃ (1.2 equiv) as the hydride source, 5 mol % Cu(OAc)₂·H₂O, and 5 mol % of various chiral bisphosphines in toluene (Table 1).⁴ Pleasingly, proof of concept was quickly established, and all ligands evaluated led to

A. Reduction of alkenylazaarenes (ref. 1)



B. Reductive coupling of alkenylazaarenes with ketones (this work)



C. Existing reductive coupling of vinylazines (ref. 10)

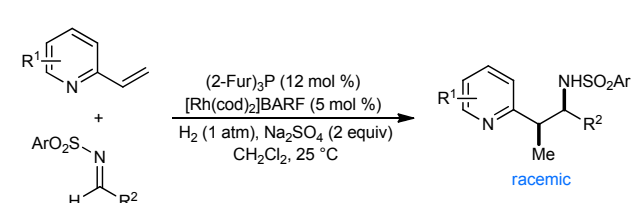
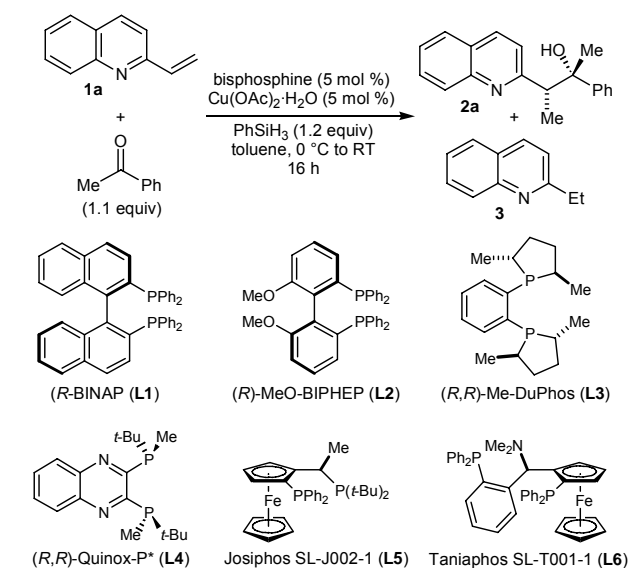


Figure 1. Catalytic transformations of alkenylazaarenes

complete consumption of **1a** to provide the coupling product **2a** as a mixture of diastereomers, along with traces of the simple reduction product **3**.¹¹ Enantioselectivities were modest using ligands **L1–L3** (entries 1–3), but high using (*R,R*)-Quinox-P* (**L4**) (entry 4), the Josiphos ligand **L5** (entry 5), and the Taniaphos ligand **L6** (entry 6). However, no diastereoselectivity was observed in most cases, with the notable exception being the reaction using **L6** which provided **2a** in 5:1 dr and 93% ee for the major isomer (entry 6). Accordingly, **L6** was selected for further experimentation.

Chart 1 presents results of reductive coupling of various vinylazaarenes **1a–1h**¹² with a range of ketones. Gratifyingly, the scope of the process is broad, and the enantioselectivities of the products were uniformly high (89–>99% ee).¹¹ Although **L6** provided the best results for products **2a–2i**, this ligand resulted in a low yield in the attempted synthesis of **2j**, and poor diastereo- and enantioselectivities in the attempted syntheses of **2k** and **2l**. In these cases, (*R,R*)-Quinox-P* (**L4**) was superior for **2j** and **2k**, and the Josiphos ligand **L5** was optimal for **2l**. In addition to **1a**, effective substrates include

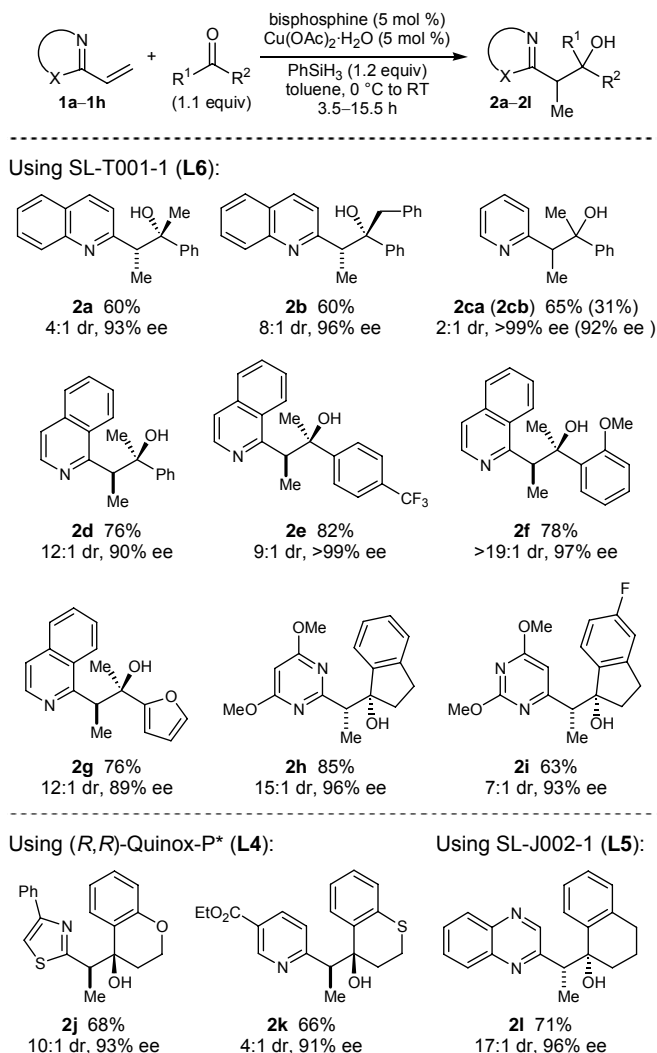
Table 1. Evaluation of Chiral Bisphosphines^a


entry	bisphosphine	2a:3 ^b	dr ^b	ee (%) ^c
1	L1	11:1	1:1	43, 50
2	L2	13:1	1:1	67, 67
3	L3	24:1	1:1	27, 17
4	L4	17:1	1:1	-60, -92
5	L5	12:1	1:1	92, 93
6	L6	7:1	5:1	93, 60

^a Reactions were conducted using 0.10 mmol of **1a**. ^b Determined by ¹H NMR analysis of the unpurified reaction mixtures. ^c Determined by chiral HPLC analysis.

those containing azines such as pyridines (products **2c** and **2k**), isoquinoline (products **2d–2g**), two different isomeric dimethoxyypyrimidines (products **2h** and **2i**), and quinoxaline (product **2l**). A vinylthiazole also smoothly underwent the reaction (product **2j**). With acyclic ketones, the diastereoselectivity of the reaction appears to be dependent on the steric properties of the azaarene, with diastereoselectivity increasing from pyridine to quinoline to isoquinoline (compare diastereomeric ratios for products **2c**, **2a**, and **2d**). In the coupling of 2-vinylpyridine with acetophenone, the two diastereomeric products **2ca** and **2cb** were isolated with high enantioselectivities (>99% and 92% ee, respectively). Regarding the electrophile, the process is tolerant of acyclic ketones containing various alkyl, aryl, or heteroaryl substituents (products **2a–2g**). In addition, cyclic ketones are viable substrates, as exemplified by the successful use of two indanones (products **2h** and **2i**), 4-chromanone (product **2j**), 4-thiochromanone (product **2k**), and tetralone (product **2l**).

Interestingly, the absolute stereochemistries of isoquinoline-containing products **2d–2g** are opposite to those of quinoline-containing products **2a** and **2b**, even though the same enantiomer of ligand **L6** was employed throughout.¹¹ In addition, the diastereochemical outcomes of the reactions producing **2h–2l** are different from those resulting in **2a**, **2b**, and **2d–2g**.¹¹ Assuming that the reactions proceed via Zimmerman–Traxler-type transition states where the larger aryl group of the ketone occupies a pseudoequatorial position,¹³ Figure 2 depicts conformations that are consistent with these observations. The stereochemical outcomes of the reactions producing **2a**, **2b**,

Chart 1. Reaction Scope with Vinylazaarenes^a


^a Reactions were conducted using 0.30–0.40 mmol of **1a–1h**. Cited yields are of pure isolated major diastereomers. Diastereomeric ratios were determined by ¹H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by chiral HPLC analysis.

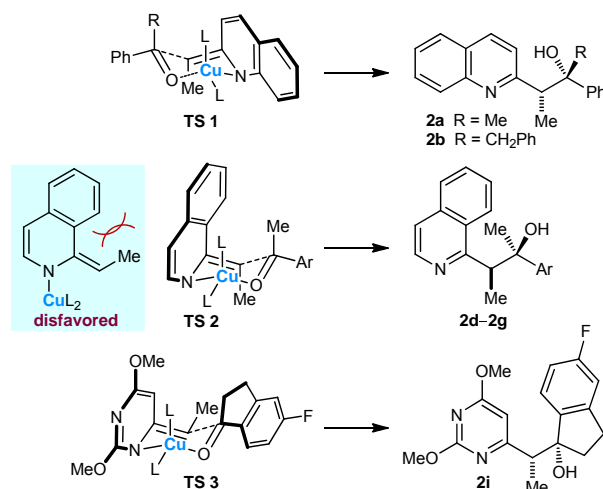
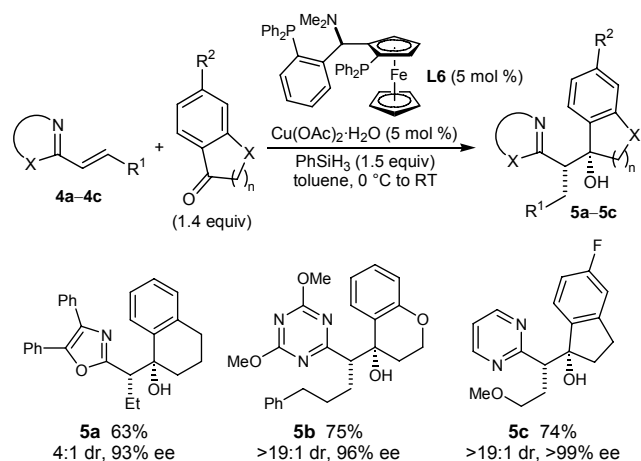

Figure 2. Rationalization of stereochemical outcomes.

Chart 2. Reductive Coupling of β -Substituted Alkenylazaarenes with Ketones^a



^a Reactions were conducted using 0.30 mmol of **4a–4c**. Cited yields are of pure isolated major diastereomers. Diastereomeric ratios were determined by ¹H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by chiral HPLC analysis.

and **2d–2g** are consistent with the participation of *Z*-azaallylcopper species¹⁴ (**TS 1** and **TS 2**), though the reasons for the opposite sense of enantioinduction in **TS 2** compared with **TS 1** are not clear at this time. Furthermore, while the preference for the *Z*-azaallylcopper species in **TS 2** is readily explained by the severe *A*_{1,3}-strain¹⁵ that would disfavor the corresponding *E*-azaallylcopper species, a similar argument cannot be used to explain the same preference in **TS 1**. For reactions producing **2h–2l**, reaction through the *E*-azaallylcopper species (or *Z*-azaallylcopper species in the case of **2j**) appears to be favored, as in **TS 3** for the formation of **2i**. The interplay between the steric and/or electronic properties of the alkenylazaarene and ligand, and the resulting effect on the stereochemical outcome, are clearly complex. In addition, while the preceding discussion has been based upon the assumption that chair-like transition states are operative, reaction through boat-like structures cannot be excluded.

Notably, the process is not limited to vinylazaarenes; β -substituted alkenylazaarenes are also effective coupling partners (Chart 2). For example, alkenylazaarenes **4a–4c**¹² containing methyl, phenethyl, or allylic ether groups smoothly undergo reductive coupling to deliver products **5a–5c**, respectively, in high enantioselectivities.¹¹ Furthermore, these products contain additional examples of azaarenes not utilized in Chart 1, such as diphenyloxazole (product **5a**), a dimethoxytriazine (product **5b**), and 1,3-pyrimidine (product **5c**).

In summary, we have described the first examples of catalytic enantioselective reductive couplings of alkenylazaarenes. The scope of this process is broad, with eleven different types of azaarenes and a range of acyclic and cyclic ketones having been shown to be effective coupling partners. β -Substitution on the alkene is tolerated, and the reactions proceed under mild conditions to deliver products in good to high levels of diastereo- and enantioselection. These features should be advantageous for application of this process in the preparation of novel enantioenriched chiral azaarene-containing building blocks.

Supporting Information. Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in cif format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) Where indicated, the relative and absolute stereochemistries of the products obtained herein were assigned by analogy with those of products **2a**, **2b**, **2d**, **2e**, **2j**, and **5c**, which were determined by X-ray crystallography using a copper radiation source (see Supporting Information for details). The stereochemistry of **2l** (obtained using ligand **L5**) was assigned by analogy with the product obtained using ligand **L6**, which was the same major enantiomer of **2l** but in 2:1 dr and 73% ee.

(12) See Supporting Information for the structures of **1b-1h** and **4a-4c**.

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